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Method and device for improving the permeability of the human skin

Description:

The invention relates to a method for improving the permeability of the human skin for transdermal delivery of active substances, by means of a plaster which is transparent in at least some areas, contains active substance, and is flexible in at least some areas, and by means of at least one external light source.

Transdermal therapeutic systems have been in established use for years in the treatment of various topical and systemic diseases. Active substances such as nicotine, estradiol, nitroglycerin, and fentanyl, for example, can in this way be administered in a more targeted manner than is possible when they are taken orally, because of the much improved pharmacokinetics and avoidance of the first-pass effect. However, the choice of active substances suitable for transdermal delivery is limited. Although transport is possible in the case of some active substances, the formulations nevertheless require an impractically large surface area.

One possible solution to the problem lies in permeation enhancers. These enhancers, for example ethanol, butanol, and other short-chain alcohols, are chemical substances which are added to the formulation in order to temporarily increase the permeability of the human skin. A sufficiently high flow rate of the pharmaceutical active substance is thereby permitted. However, these enhancers are taken up by the body and place a burden on the metabolic processes of the body.

Therefore, the present invention is based on the object of developing a method for improving the permeability

of the human skin, which method, without causing systemic effects, permits a reproducible permeability for certain active substances.

This object is achieved by the features of the main claim and independent claim 3. Light emitted at least briefly from an external light source and impinging normally with respect to the plaster, in at least some areas, is focussed through a multiplicity of individual positive lenses, integrated in the plaster, onto the stratum corneum of the skin, in order in this way to generate stratum corneum changes which improve the permeability of the skin.

For this purpose, the plaster comprises at least one top layer and at least one active-substance-containing self-adhesive layer. The top layer and the active-substance-containing layer are transparent in at least some areas, the transparent areas lying over one another inside the plaster, and the top layer comprising a multiplicity of optical positive lenses organized in a planar arrangement.

The transdermal therapeutic system thus comprises, inter alia, at least one active-substance-containing matrix layer directed toward the skin, and a transparent, geometrically contoured top layer. The system is affixed temporarily to the skin in the form of a plaster. Such an arrangement permits the use of light sources for improving the transdermal absorption during the period when the plaster is being worn.

Further details of the invention are set forth in the dependent claims and in the following description of schematically illustrated embodiments.

Figure 1 shows a plaster and stratum corneum in cross section;

Figure 2 shows a partial top view of a lens array without the plaster edge;

Figure 3 shows the same as Figure 1, but with lenses of different focal lengths;

Figure 4 shows the same as Figure 1, but with mechanical extraneous light shading.

Figure 1 illustrates a physical method by which the transdermal delivery of active substance is greatly accelerated. For this purpose, for example, a self-adhesive plaster (10) is used which has a transparent top layer or backing layer (12, 13) and at least one active-substance-containing and likewise transparent adhesive layer or matrix layer (50, 40). The top layer (12) comprises an array of optical lenses (20-22). The plaster (10) affixed to the skin (6) is illuminated at least briefly by a light source (1) having a high intensity of illumination. The light (2) impinging at least almost normally with respect to the rear face (14) of the plaster is separately focused by the individual positive lenses (20-23) and projected onto the stratum corneum (7) of the skin (6). At the individual focal points or focal lines, small focal spots (8) are created which keep the stratum corneum (7) thin and open for transport of active substance. The focal lines arise because of the diacaustic of the positive lenses.

The matrix layer and/or adhesive layer (40, 50) here constitute an active substance depot which is able to release its active substance over hours or days, for example.

The plaster (10) stored prior to use is protected from unwanted release of active substance, or from loss of active substance, by at least a protective film adhering to the adhesive layer (50).

The top layer (12) is in this case a transparent film, for example, in which a large number of small lenses (20) are integrated. Each individual lens (20) has, for example, a double convex shape, of which the centers of curvature each lie on an optical axis (23). The individual optical axes (23) are generally oriented normally with respect to the particular surface element of the rear face (14) of the plaster. The distance between the optical axes (23) of two adjacent lenses (20) is 50 to 500 µm, for example. In certain cases, the respective distance can be increased to one millimeter. The focal length of the individual lenses (20) is dimensioned, taking account of the possibly different indices of refraction of the lens material and of the matrix materials, such that the mean focal length of ca. 10 to 20 µm lies under the outer face (9) of the skin (6) in the stratum corneum (7). For example, with a top layer (12) having a thickness of 40 µm and a matrix and adhesive layer (40, 50) having a thickness of 100 µm, the mean focal length is thus 135 µm.

Radially, the lenses (20) according to Figure 2 are delimited, for example, by the perimeter face (25) of a straight, regular and hexagonal prism. A complete lens (20) would have the circular outer contour (26) shown in Figures 1 and 2. Alternatively, the lenses (20) can also each have a cylindrical outer contour. The resulting interstices would then be filled by plane surfaces, for example. The mean thickness of the flexible film (12) containing the lenses (20) is ca. 40 - 100 µm. The total surface area of the transparent part of the plaster (10) is, for example, between 2 and 50 cm^2, depending on the application in question.

In applications in which the illumination results in a visible partial tinting of the stratum corneum, the lenses in the outer plaster areas can, for example, be

made partially opaque or can be made without a convex curvature in order to reduce the transition contrast from untinted to tinted stratum corneum, for example for cosmetic reasons.

This principle can of course also be reversed. Thus, a tanned pattern in the form of a temporary tattoo can be produced on the stratum corneum by means of a specific arrangement of lenses, generating focal points, and of optically inactive interstices.

Possible materials for the top layer are: polycarbonate, polyethylene, polymethyl methacrylate, polyethylene terephthalate and other polyesters, polypropylene, acrylate polymers, polyamides, and inorganic glasses or the like, provided these materials have optically refractive and transparent properties.

Since high demands are not generally placed on the optical quality of the lens arrays, the film (12) can, for example, be produced by injection molding. In the case of micro-lens arrays with smaller than average lenses, the film (12) can also be produced by microlithography.

According to Figure 3, lenses (20-22) of different focal lengths can be arranged in a lens array. In the illustrative embodiment, three different lenses (20, 21, 22) are used which are arranged, for example, in a uniform distribution within the lens array. Their focal lengths vary in a range of from 10 to 50 μm, for example. With the aid of such a lens array, a thicker stratum corneum can temporarily be made more permeable.

In Figure 4, a plaster is shown whose top layer (13) corresponds for example to three to four times the thickness of the material of the top layer (12) from Figure 1. Here, the rear convex surfaces (31) of the individual lenses (20) each form the bottom of a blind

hole (32) that has been let into the top layer (13). The inner surfaces (33) of the blind holes (32), except for lens surface (31), have, for example, a coating either prohibiting total reflection or permitting the latter only in the form of diffuse reflection. If appropriate, the coating is in the form of a matt black color. Light (3) impinging at an oblique angle into the blind holes (32) is then able to cause virtually no change in the skin beneath the lens.

Instead of the lens array provided with blind holes (32), it is also possible to use a lens array known from Figure 1 onto which a flexible honeycomb grid is affixed. The honeycomb grid, which is made for example from a material other than that of the lens array, comprises, for example, a multiplicity of tubes of hexagonal cross section. The center lines of the tubes are oriented substantially normal with respect to the skin surface.

Another variant for stopping extraneous light is to arrange one or more stubs on almost every individual edge of the individual lenses (20-22), said stubs being arranged substantially normal with respect to the skin surface (9). The stubs protruding from the outer face (14) of the plaster cast a shadow across the individual lens surfaces (31) in the case of extraneous light.

Another alternative for controlling the amount of light to be applied to the skin lies in the use of phototrophic glasses. Lens materials of this kind reversibly darken the lenses within the space of seconds to minutes. Complete coverage of the lens array by means of an opaque self-adhesive covering film is also conceivable.

Instead of this kind of multiple dimming, it is also possible to use lens materials which become permanently opaque or turn dark after minutes or hours, as a result

of ageing caused by the action of light.

With a defined illumination of the corresponding area of the stratum corneum supporting the plaster, the transport of active substance through the skin can be controlled in a reproducible manner. Important influencing factors here are, for example, a constant level of irradiation and a constant distance between the light source and the plaster. Since a single delivery of light energy or radiant energy at the start of treatment is in some cases insufficient, it may be necessary to configure a flash lamp which emits light impulses at defined time intervals, for example minutes or hours, to ensure that the skin structures created by the focal lens action are kept open.

List of reference numbers:

1	light source
2	light, direction of light normal with respect to plaster surface
3	light, direction of light oblique with respect to plaster surface
6	human skin
7	stratum corneum
8	focal spots, changes in stratum corneum
9	surface of the skin
10	plaster
11	plaster with partially shaded lenses
12, 13	top layer, backing layer, film
13	top layer with blind holes
14	outer face of plaster, rear face of plaster
20-22	lenses, convex lenses
23	optical axis
25	perimeter surface
26	outer contour
31	surfaces, curved
32	blind holes
33	inner face, cylindrical
40	matrix layer
50	adhesive layer